according to the invention. The invention thus also concerns corresponding processes, uses and kits. --

REMARKS

Claims 1-27, 29, 37, and 47-49 are pending in the application. Claims 28, 30, 31, and 38-46 were cancelled without prejudice in the First Supplemental Amendment, filed July 26, 2001, in view of the restriction requirement imposed by the Examiner. Claim 32 has been cancelled by this Amendment.

Claims 1, 15, 17, 18, and 33-37 and the specification have been amended in order to render the claims and the specification more fully compliant with formal requirements. No new matter is added by the amendments. Support for the amendments to claims 1 and 34-37 is found at least in each of the claims as originally filed. Support for the amendment to claim 15 and to the specification is found at least in the specification at page 25, lines 17-18, where the registered trademarks designating each of the peptide tags are provided. The amendments merely insert the generic technology signified by each of the trademarks at the time of filing, information of which a skilled person would have been readily aware. Claim 33 has been amended to correct a typographical error; the amendment adds no new matter. Support for the amendment to claim 33 is found at least in the specification at page 31, lines 1-8. Claims 17 and 18 have also been amended, and the deleted subject matter rewritten as new claims 39 and 39.

New claims 47-49 have been added. Support for each of the new claims is found at least at claims 17 and 18 as originally filed, and in the specification, at page 28

The abstract has been amended to render it more compliant with formal requirements pertaining to length.

Pursuant to 37 C.F.R. § 1.121, marked-up versions of the amended portion of the specification, of the amended claims, and of the abstract of the disclosure, showing the changes made, are enclosed herewith, each on a separate paper.

Pursuant to the rules governing sequence identifiers, the amino acid sequence of the FLAG tag has been designated in the specification as SEQ ID NO: 39. A replacement Sequence Listing (paper and computer readable copies), each containing sequence of SEQ ID NO: 39, is submitted herewith. Further, SEQ ID NOs: 5 and 6 have been amended to correct an error, as discussed in more detail at section V of this response, below. The Sequence Listing submitted herewith contains no new matter, as support for the addition of the FLAG sequence is found at least in the specification at page 25, lines 17-18, as initially filed, and support for the

amendment to the sequences designated SEQ ID NOs: 5 and 6 is found at least in the Sequence Listing as originally filed, and in Fig. 11c as originally filed.

A Statement under 37 C.F.R. § 1.821 *et seq.* is supplied.

In view of the amendments to the claims, a complete set of all pending claims, incorporating the amendments made herein, is submitted for the Examiner's convenience.

Each of the Examiner's rejections, as set forth in Paper No. 12, is addressed below in the order in which they were presented.

I. Sequence Listing

At pages 2-3 of Paper No. 17, the Examiner has stated that the application contains sequence disclosures that are not compliant with the sequence rules. Specifically, the Examiner asserts that the sequence "S4-S3-S2-S1/S1'," which is recited, *inter alia*, in claim 8, must be included in the sequence listing, in order for the application to be fully compliant. The applicants respectfully disagree with the Examiner.

The sequence rules state that "sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from [the sequence rules]". 37 C.F.R. § 1.821. "Specifically defined" means those amino acids which are precisely defined in accordance with the WIPO amino acid sequences. *Id.* In the present application, the sequence listing to which the Examiner objects is a non-specific sequence, designating five non-specific amino acids. Thus, as the objected to sequence contains fewer than four specified amino acids (in fact, it contains zero specified amino acids), it is not necessary to include this amino acid sequence in the sequence listing.

Therefore, as the application is fully compliant with the sequence rules, the applicants respectfully request that the Examiner reconsider and withdraw this objection.

II. Priority Under 35 U.S.C. § 120

At page 3 of Paper No. 17, the Examiner has stated that the subject matter claimed in claims 1-27, 29, and 32-37 is supported in the parent application, serial no. 09/347,064. However, there is inconsistent language following this statement, which the applicants believe may be an inadvertent typographical error. If the applicants' understanding is incorrect, and the Examiner intended to state that she believes that the subject matter of the above claims is not supported by the parent application, it is requested that the Examiner clarify the specific bases for such assertion in the next Office Action.

III. Priority Under 35 U.S.C. § 119

At pages 3-4 of Paper No. 17, the Examiner asserts that claims 1-37 do not have "written support" in the foreign priority document EP 97 10 0012.0 ("the EP application") as evidenced by the translation filed by the applicants on July 27, 2001. (As noted above, claims 28 and 30-32 have been cancelled.) The applicants respectfully disagree with the Examiner's statement, insofar as it applies to the pending claims.

The test for sufficiency of support in a prior application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." M.P.E.P. 2163.02, citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). The written description requirement is satisfied even if the subject matter of the claim in question is not described literally (*i.e.*, using the same terms or *in haec verba*). M.P.E.P. 2163.02.

Claims 1-27, 29, and 33:

With respect to claim 1, the Examiner has stated that the claim does not have "written support" in the EP application because of the language "at least a fragment of" with reference to SEQ ID NOs: 1, 2, 5, and 6. Claims 2-27, 29, and 33 depend from claim 1, and, consequently are similarly deficient according to the Examiner. The applicants disagree.

In the prior application, as evidenced by the translation supplied on July 27, 2001, the subject matter of claims 1-27, 29, and 33, is fully supported, as it reasonably conveys to the skilled artisan that the applicants were in possession of nucleotides having "at least a fragment of" to SEQ ID NOs: 1, 2, 5, and 6. Fig. 11.a of the EP application discloses the nucleotide sequence and derived amino acid sequence of rMLA. Similarly, Fig. 11.c of the EP application discloses the nucleotide sequence and derived amino acid sequence of the rML propeptide. The EP application discloses that, in a preferred embodiment, the invention relates to a nucleic acid molecule wherein the mistletoe lectin A-chain is encoded by a nucleic acid molecule. This nucleic acid molecule can, according the EP application, be selected from: (i) nucleic acid molecules which comprise a nucleic acid sequence encoding the amino acid sequence in Fig. 11.a (rMLA) or a fragment of rMLA; (ii) nucleic acid molecules which comprise the nucleotide sequence indicated in Fig. 11.a (rMLA) or a fragment of rMLA. (EP application, English language translation, at page 9, lines 24-28) Thus, the disclosure of the EP application conveys

that the nucleic acid molecule can be a fragment of the nucleic acid sequence of rMLA or a fragment of a nucleic acid molecule encoding rMLA, either alone or included in a nucleic acid sequence having other nucleotides, the identity of which is not significant.

Similarly, the EP application discloses that the mistletoe lectin A can be the mistletoe lectin propeptide (rML), where the propeptide is encoded by a nucleic acid molecule. The prior application discloses that this nucleic acid molecule can be chosen from any of the following: (i) nucleic acid molecules comprising a nucleotide sequence encoding the amino acid sequence indicated in Fig. 11.c (rML) or encoding fragments of the amino acid sequence of rML and (ii) nucleic acid molecules comprising the nucleotide sequence indicated in Fig. 11.c (rML) or fragments of this nucleic acid sequence. (EP application, English language translation at page 10, lines 5-7).

In the present application, SEQ ID NO: 1 is the nucleotide sequence of rMLA and SEQ ID NO: 2 is the derived amino acid sequence of rMLA. Further, SEQ ID NO: 5 is the nucleotide sequence of the rML-propeptide and SEQ ID NO: 6 is the derived amino acid sequence of the same. Thus, the disclosure of the EP application provides support for those portions of the present claims reciting "at least a fragment of" with reference to SEQ ID NOs: 1, 2, 5, and 6, at least as shown in Table I below:

TABLE I

Claim Language	*Supporting Disclosure in EP Application*
. . . a nucleic acid molecule having the nucleotide sequence of at least a fragment of SEQ ID NO: 1	Page 9, lines 27-28 : "nucleic acid molecules which comprise the nucleotide sequence indicated in Fig. 11.a or a fragment thereof"
. . . at least a fragment of a protein having the amino acid sequence SEQ ID NO:2	Page 9, lines 24-26: "nucleic acid molecules which comprise a nucleotide sequence encoding the amino acid sequence indicated in Fig. 11.a or a fragment thereof"
. . . a nucleic acid molecule having the nucleotide sequence of at least a fragment of SEQ ID NO:5	Page 10, lines 6-7: "nucleic acid molecules comprising the nucleotide sequence indicted in Fig. 11.c or a fragment thereof"
. . . at least a fragment of a protein having the amino acid sequence SEQ ID NO: 6	Page 10, lines 3-5: "nucleic acid molecules which comprise a nucleotide sequence encoding the amino acid sequence indicated in Fig. 11.c or a fragment thereof"

Claims 2 and 3:

With regard to claims 2 and 3, the Examiner states that use of the language "has at least one" with reference to amino acid deletions, substitutions, insertions, additions or exchanges, does not have written support in the written description of the prior application. The applicants disagree with the Examiner's assertion. The applicants direct the Examiner to page 10 of the translation of the EP application, wherein the EP application states "the effector module comprises an allele or a derivative of mistletoe lectin A-chain by amino acid deletion, substitution, insertion, addition, and/or exchanges and the processing module . . . comprises an allele or derivative of the mistletoe lectin propeptide by amino acid deletion, substitution, insertion, addition, and/or exchanges."

Claim 5:

With respect to claim 5, the Examiner asserts that the language "encodes at least a fragment of" and "of at least a fragment" with respect to SEQ ID NOs: 3 and 4 does not have written support in the EP application. This is incorrect. SEQ ID NOs: 3 and 4 of the present

application are the nucleotide sequence and the derived amino acid sequence of rMLB, respectively. In the EP application, the nucleotide sequence and derived amino acid sequence of rMLB are disclosed at least in Fig. 11.b. At pages 11-12 of the translation of the EP application, it is disclosed that, in a preferred embodiment, the invention relates to a nucleic acid molecule having a modulator module. The modulator module is encoded by a nucleic acid molecule, which itself may be selected from nucleic acid molecules which comprise a nucleotide sequence encoding the amino acid sequence of Fig. 11.b (rMLB), or a fragment thereof, and nucleic acid molecules which comprise the nucleotide sequence of Fig. 11.b (rMLB), or a fragment thereof. Thus, similar to the situation with claims 1-27, 29, and 33-37 above, use of the term "comprising" conveyed to a person of skill that the applicants were in possession of the invention as recited in the present claim 5, at the time of filing of the priority document.

Claim 6:

With regard to claim 6, the Examiner asserts that the language "has at least one" with respect to amino acid deletions, substitutions, insertions, additions, or exchanges, does not have support in the priority document. The applicants respectfully disagree with the Examiner. Support for this claim element is found at least in the prior application at page 12 of the EP application, where it is specified that the nucleic acid molecule is an allele or derivative of mistletoe lectin B by amino acid "deletion, substitution, insertion, addition, and/or exchanges," indicating that more than one may be present.

Claim 17:

The Examiner states that the recited amino acid exchanges at positions "68, 70, 75, and 249" do not have written support in the prior application. Again, the applicants respectfully disagree with the Examiner, and direct him to page 17 of the translation of the prior application, where it is disclosed that the mistletoe lectin B chain exhibits an exchange at amino acid residue position 249. With regard to exchanges at positions 68, 70, and 75, while the applicants do not necessarily agree with the Examiner, those positions have been deleted from claim 17. Accordingly, the Examiner's assertion is no longer applicable to claim 17.

Claim 18:

With respect to claim 18, the Examiner argues that the language "substitution of S at position Y68, substitution of S at position Y70, substitution of S at position Y75" and "substitution of S at position F79" do not have support in the EP application. While not necessarily agreeing with the Examiner, these portions of claim 18 have been deleted. Therefore, the Examiner's rejection is no longer applicable to claim 18.

Claim 32:

With respect to claim 32, the Examiner asserts that there is no support for the medicament recited in claim 32. Claim 32 has been cancelled without prejudice. Thus, the Examiner's rejection is no longer applicable.

Claims 34-37:

The Examiner contends that claims 34-37 are not supported by written description of the EP application, on the identical grounds that he has asserted with regard to claims 1-33. Accordingly, the same argument is applicable.

For the reasons discussed above, all the subject matter recited in claims 1-27, 29, and 32-37 of the present application is fully supported in the prior application, and therefore properly claims the benefit of the priority date of January 2, 1997. It is requested that the Examiner withdraw the objection and confirm that each of claims 1-27, 29, and 32-37 is entitled to the priority date.

IV. Objection to Abstract

At page 4, Paper No. 17, the Examiner has objected to the abstract for containing more than 150 words. The abstract has been replaced by an abstract containing fewer than 150 words. Accordingly, it is requested that the Examiner reconsider and withdraw her objection, as it is no longer applicable.

V. Rejection Under 35 U.S.C. § 112 - Alleged introduction of new matter by correction of the sequence listing

At pages 5-6 of Paper No. 17, the Examiner has asserted that the corrected sequence listing, filed by Amendment on February 28, 2000, introduces new matter because it includes the SEQ ID NOs: 5 and 6 which differ from the SEQ ID NOs: 5 and 6 originally filed.

Thus, the Examiner has rejected claim 1-27, 29, and 32-37, all of which recite SEQ ID NOs: 5 and 6 for containing new matter. To remedy this deficiency, the Examiner asserts that the applicant is required to submit a declaration attesting that the changes made to the sequence were obtained by sequencing the identical source material. The Examiner's rejection is no longer applicable.

The sequence listing submitted by applicants on February 28, 2000, changed SEQ ID NOs: 5 and 6 to designate the sequences shown in Figs. 11c' as originally filed (therefore such sequences are not new matter). However, in this response, SEQ ID NOs: 5 and 6 have been

amended. "SEQ ID NO: 5" now designates a nucleotide sequence identical to the sequence designated SEQ ID NO: 5 when the application was filed (and which is shown in Fig. 11c). Similarly, "SEQ ID NO: 6" is now designating a primary amino acid sequence identical to the nucleotide sequence designated SEQ ID NO: 6 in the originally-filed Sequence Listing (which is also disclosed in Fig. 11). Therefore, the Examiner's rejection of claims is no longer applicable, and its withdrawal is requested.

VI. Rejection Under 35 U.S.C. § 112, First Paragraph - For alleged lack of enablement

At pages 6-7 of Paper No. 17, the Examiner has rejected claim 32 under 35 U.S.C. § 112, first paragraph, asserting that claim 32 contains subject matter which is not enabled by the specification. Claim 32 has been cancelled. Therefore, the Examiner's rejection is no longer applicable. Its reconsideration and withdrawal are requested.

VII. Rejection Under 35 U.S.C. § 112, First Paragraph - For alleged lack of enablement

At pages 8-10 of Paper No. 17, the Examiner rejects claims 1-27, 29, and 32-37 under 35 U.S.C. § 112, first paragraph, asserting that portions of such claims are not enabled by the specification. Specifically, the Examiner states that the specification does enable "a nucleic acid encoding a fusion protein consisting of: (a) an effector module consisting of SEQ ID NO: 1, (b) a processing module consisting of SEQ ID NO: 5, (c) a targeting module consisting of bFGF, (d) a modulating module consisting of SEQ ID NO: 3, and (e) an affinity module consisting of SEQ ID NO: 17. However, according to the Examiner, the specification does not reasonably provide enablement for: (a) nucleic acids encoding fusion protein fragments, (b) nucleic acid molecules encoding fusion protein derivatives, (c) nucleic acid molecules which hybridize to the fragments and derivatives of (a) and (b) (*i.e.*, or the complements of such nucleic acids), and (d) "nucleic acids . . . encoding fusion proteins containing amino acid deletions, substitutions, insertions, additions or exchanges."

As basis for this rejection, the Examiner argues that the disclosure in the specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation, *i.e.*, that the scope of the claims is not commensurate with the enablement provided by the disclosure. The deficiency of the specification, according to the Examiner, is that it fails to provide sufficient guidance regarding the specific properties required to determine whether a polypeptide encoded by the claimed nucleic acid is a functional effector, processing, modulating, targeting, or affinity module. To

support this broad statement, the Examiner cites several references which allegedly state that even minor variations in the sequences of polypeptides and/or nucleic acids can result in significant alterations in structural and chemical behavior and therefore, according to the Examiner, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing such predicted structural determinations to ascertain binding and/or functional aspects and what changes can be tolerated with respects thereto is complex and well outside the realm of routine experimentation. Therefore, according to the Examiner, the specification does not enable the full scope of the claims.

The Examiner argues that such claims 25 and 26 are not enabled, as the specification discloses that efficient intracellular protease cleavage requires unglycosylated proteins, such as those produced in prokaryotic cells. Thus, according to the Examiner, claims 25 and 26, which are drawn to nucleic acids in eukaryotic glycosolating hosts are not enabled. The applicants respectfully traverse the Examiner's rejection of claims 1-27, 29, and 32-37 as lacking enablement on these grounds for the reasons set forth below.

First, contrary to the Examiner's assertion, none of the claims is drawn to nucleic acids encoding fragments or derivatives of fusion proteins. Each of the claims is drawn to a nucleic acid encoding a fusion protein, which is itself made up of at least four portions or "modules." Thus, the Examiner's assertion that the specification does not enable a skilled artisan to make or use fragments/derivatives of the claimed fusion proteins is irrelevant and inapplicable, and therefore it will not be further addressed herein.

The Examiner contends that the specification fails to enable the full scope of the claims and therefore does not provide sufficient information, such that a person of skill could make and use the invention without undue experimentation. In particular, it appears the Examiner's position is as follows: (1) the recitation of modules encoded by nucleic acids which comprise fragments and derivatives of specific nucleic acid sequences, and of modules comprising amino acid sequences having "deletions," "substitutions," "insertions", "additions," and "exchanges", results in claims encompassing more than is enabled in the specification; and (2) such compositions are not enabled, as the specification fails to provide sufficient guidance regarding the specific process properties required to determine whether the claimed nucleic acid encodes a functional effector, processing, modulating, targeting, or affinity module in the absence of undue experimentation, given the alleged unpredictability of the art. The Examiner's reasoning is incorrect.

First, the Examiner misunderstands the scope of the claims. Modules of the fusion protein which are encoded by the claimed nucleic acid molecule having "fragments," "derivatives," "deletions," "substitutions," "insertions," "additions," and "exchanges" (hereinafter collectively referred to as "fragments, etc."), are the effector module, the processing module, and the modulator module. No fragments, etc., are presently recited as being include in the portion of the nucleic acid molecule encoding the targeting module or the affinity module. (Although the applicants firmly believe such encoding fragments, etc.- are enabled, they are not recited in the present claims; therefore, a discussion of their enablement is not discussed herein.)

Second, guidance which is at least adequate to instruct the person of ordinary skill in the art regarding the specific properties of the nucleic acid molecules encoding a functional effector, processing, or modulating modulator is provided in the specification. The function of the effector module is expressly articulated at least at pages 11-12 of the specification. The functions of the processing module and the modulator module are found at least at page 13, lines 1-14, and page 17, line 21 to page 18, line 11, respectively. Further information pertaining to means of determining whether a given protein exhibits the desired functionalities or properties is set forth in Examples 1 to 13. In addition, the structures disclosed in the specification provide the skilled artisan with a concrete starting point from which variants can be made using standard techniques. These teachings supplied by the specification provide the ordinarily skilled artisan criteria which, combined with well-established techniques and knowledge well known in the art, allow her to ascertain nucleic acid molecules which encode modules having the desired properties. Therefore, such teachings provide enablement of the full scope of all of the claims under U.S. patent law. *See, e.g.,* M.P.E.P. 2164.06, citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1998) ("The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification . . . provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed.") (emphasis added).

The Examiner argues that any experimentation would be "undue," because of the "unpredictability" of the art and cites several references showing that substitutions in the sequence of amino acids and/or nucleotide sequences can have effects on the function of the peptide and/or that the a given sequence of a nucleic acid molecule does not provide sufficient information to predict the structure of the protein. However, although the applicants do not dispute the general technical statements set forth in these references, the Examiner's application of the "unpredictability of the art" factor of *Wands* is erroneous and, consequently, neither

correctly nor usefully aids in the present analysis under § 112. The *Wands* unpredictability factor, properly applied, allows evaluation of whether the techniques and technologies that an ordinarily skilled artisan may utilize in his practice of the invention are well established, well understood, and provide consistent reproducible results. *See,* M.P.E.P. 2164.06, (providing a discussion of *In re Wands*). In the present application, the predictability of screening techniques for evaluating the functional properties of proteins or peptide fragments is well established in the art, and easily reproduced by a person of skill, particularly given the structures disclosed in the specification. Accordingly, applied properly, this factor of *Wands* analysis favors the applicants.

Further, contrary to the position of the Examiner, there is no requirement under § 112, *Wands*, or any other patent statute or rule, that applicants inform the person of ordinary skill as to how to "predict" the precise structure of each and every molecule which falls within the scope of a given claim. An applicant is entitled to claim his inventive technology by any means of his choosing, which includes claims that recite both structure and/or function. *See,* M.P.E.P. 2173.01. The Examiner cannot require the applicants to recite every structure within the scope of the claims; it is enough that the applicants have provided a limited universe of structures (*e.g.,* a nucleic acid encoding a fragment of protein having a sequence of SEQ ID NO: 2). The criteria by which the proteins having the desired properties can be easily and routinely ascertained.

Finally, the Examiner reasons that claims 25 and 26 are not enabled because the specification does not, in the Examiner's view, provide support for glycosylated fusion proteins (expressed by the eukaryotic host cells recited in claims 25 and 26). To the contrary, the specification in combination with the relevant art of which a skilled artisan has knowledge, provides guidance as to how to make and use the invention of claims 25 and 26 (*see, e.g.,* pages 27, lines 19-24, where disclosure is provided indicating that the claimed fusion proteins can be produced in eukaryotic cells). Similar to the modules encoded by the nucleic acids comprising fragments, etc., discussed above, any fusion protein produced, regardless of its glycosylation state, or the host cell from which it is generated, can be routinely screened to determine whether it had the recited properties. Thus, a person of skill is easily and routinely able to determine how to make and use any vector within the scope of claims 25 and 26.

In view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw his § 112, first paragraph, rejection of claims 1-27, 29 and 34-37.

VIII. Rejection Under 35 U.S.C. § 112, First Paragraph - For alleged lack of written description

At page 11 of Paper No. 17, the Examiner has rejected claims 1-27, 29, and 32-37 under 35 U.S.C. § 112, first paragraph, asserting that these claims are not supported by a written description in the specification which reasonably conveys to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. The Examiner states that the applicant was in possession of a nucleic acid encoding a fusion protein "consisting of": (a) an effector module consisting of SEQ ID NO:1, (b) a processing module consisting of SEQ ID NO: 5, (c) a targeting module consisting of bFGF, (d) a modulating module consisting of SEQ ID NO: 3, and (e) an affinity module consisting of SEQ ID NO: 17. However, the Examiner asserts that there is insufficient written description in the specification to show that the applicant was in possession of a nucleic acid encoding a fusion protein comprising (a) a "fragment" or "derivative" of the mistletoe lectin A-chain (claims 1 and 37), (b) a "fragment" or "derivative" of the mistletoe lectin B-chain (claim 16), and (c) a "fragment" or "derivative" of the mistletoe lectin propeptide (claims 1 and 36).

Additionally, the Examiner asserts that there is insufficient definition in the specification for "hybridize" and "degenerate", thus, a person of skill would not have sufficient guidance as to how to identify those nucleic acids which "hybridize" and are "degenerate", "other than trial and error in an *in vitro* assay". Therefore the Examiner states "the skilled artisan cannot envision all of the contemplated nucleic acid and amino acid sequence possibilities recited in the instant claims."

The Examiner also argues that the specification defines "fragment" only for the mistletoe A-chain and then only as a peptide "which exhibits intracellular toxic activity", and the specification, in the view of the Examiner, fails to define "derivative." Therefore, the Examiner concludes that one of skill would recognize that the specification fails to disclose a representative number of species to described the claimed genus. The applicants traverse these rejections.

The written description requirement requires that the applicants' specification convey with reasonable clarity to those skilled in the art that, as of the filing date, he or she was in possession of the invention, *i.e.*, whatever is now claimed. M.P.E.P. 2163, citing *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d 1555, 1563-64 (Fed. Cir. 1991). It is well settled that the claims as filed in the original specification are part of the disclosure. *See,* M.P.E.P. 2163.06. Each of the claims 1-27, 29, and 32-37 is a claim which was present in the original application as filed, with the exception of a few corrected typographical errors. The particular sequences identified by the Examiner were originally disclosed and this information would have placed the skilled artisan in

possession of fragments. Etc., in view of the level of skill in the art. It is respectfully requested that the Examiner reconsider and withdraw this rejection.

IX. Rejection Under 35 U.S.C. § 112, First Paragraph - For alleged lack of antecedent basis

At page 13, the Examiner objects to the specification as failing to provide proper antecedent basis for the claimed subject matter. Specifically, the Examiner asserts that claim 8 which recites, in relevant part, "[and] neither S3 nor S4 is proline, and S1' is any amino acid residue" is not disclosed in the specification. Additionally, the Examiner objects to the language used in claim 17 which recites "amino acid changes at position 68, 70, 75, 79, and 249." The Examiner asserts that such elements are not disclosed in the specification. At page 13, the Examiner has objected to claims 35 and 37, asserting that such claims fail to recite SEQ ID NOs in the claims. The applicants respectfully traverse this rejection.

This rejection is not proper; consequently, the applicants are unable to address it in a meaningful way. Rejections for "lack of antecedent basis" are rejections of the claims, and are properly made under 35 U.S.C. § 112, second paragraph. All of the pending dependent claims have proper antecedent bases. It is respectfully requested that the Examiner reconsider and withdraw this rejection.

The applicants respectfully point out that claims 35 and 37 have been amended to include the correct SEQ ID NOs. Accordingly, even if this were a proper rejection, this portion of it is no longer applicable.

X. Rejection Under 35 U.S.C. § 112 - For alleged indefiniteness

A. At pages 13-14, the Examiner has rejected claims 1-27, 29 and 32-37 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, the Examiner asserts that the elements "a nucleic acid molecule which hybridizes" and a nucleic acid molecule which is "degenerate" are indefinite. The applicants respectfully traverse this rejection.

The term "a nucleic acid molecule which hybridizes" is not indefinite. A person of ordinary skill, upon review of the specification, would have an understanding of what was meant as hybridization techniques were well known in the art, at the time the application was filed. Further, such techniques are described in the specification at least at page 16, lines 17-25.

With regard to the term "degenerate" when referring to a nucleic acid molecule, the applicants assert that such claim has a definite meaning to a person of ordinary skill in the

art. A person skilled in the art would easily understand that this term is indicative of a codon which, while not having the same nucleotide sequence as a second codon, encodes the same amino acid as the second codon. *See, e.g.,* The Oxford Dictionary of Biochemistry and Molecular Biology, Smith et al., Eds., Oxford University Press, 1997 at page 161 (a copy of which is enclosed with this Office Action); *see, also,* Lewin, B., Genes IV, Oxford University Press (1990) at page 119 ("A striking feature of the [genetic] code is its degeneracy: 61 codons represent 20 amino acids.") (emphasis in original).

Accordingly, for the reasons given below, it is respectfully requested that the Examiner reconsider and withdraw his 35 U.S.C. § 112 rejection with regard to the above-discussed terms.

B. At pages 13-14 of the Office Action, the Examiner has maintained the rejection of claims 1, 5, 8, 10, 11, 13, 14, 16, 34, and 36 under 35 U.S.C. § 112, second paragraph, asserting such claims are indefinite for use of the terms "degenerate", "a cell of the specific immune system", "a degenerate cell of the immune system", and "use of the symbol '/' and the designation 'S1'", as the rejection was set forth in Paper No. 9, mailed May 24, 2000. The applicants respectfully traverse these rejections.

First, the Examiner has asserted, in Paper No. 9, that the term "degenerate" has only a vague meaning and renders the claims in which it is used indefinite. As discussed above, the contrary is true. The term "degenerate", as applied to nucleic acids that encode a polypeptide, has a well understood meaning known in the art, as discussed above. A person skilled in the art would easily understand that this term is indicative of a codon which, while not having the identical nucleotide sequence of a second codon, encodes the same amino acid as the second codon. *See, e.g.,* The Oxford Dictionary of Biochemistry and Molecular Biology, Smith et al., Eds., Oxford University Press, 1997 at page 161 (a copy of which is enclosed with this Office Action). Also on Paper No. 9, the Examiner has made the indefiniteness rejection based upon the use of the phrase "a cell of the specific immune system" and of the converse phrase used by the applicants "cells of the unspecific immune system." Asserting such terminology renders the claims indefinite. A person skilled in the art would understand that a cell of the "specific immune system" refers to an immune cell which expresses an antigen specific protein on its surface, as the language "specific immune response" is commonly used to indicate immunity implicating an immune response involving the specific recognition of an antigen by antibodies. Similarly, a person of skill would also understand that the converse term "unspecific immune system" refers to what is sometimes termed in the art as "non-specific immune

response," also a term having a well established meaning in the art. *See, e.g.,* Golub et al., Immunology: A Synthesis, 2nd ed., Sinaur Assoc., Inc., Sunderland, Massachusetts (1991) at pages 7-8, a copy of which is enclosed for the Examiner's review. The applicants submit that the use of the term "unspecific" instead of "non-specific" is an artifact of a slightly inartful translation of the application from the original German, but note that such minor discrepancy of translation is insignificant and inconsequential to one versed in the art, as the meaning is clear from both the implied definitions provided in the specification and the references made to the "specific" immune system in the specification. *See, e.g.,* page 25, lines 10-15 of the specification.

Additionally, in Paper No. 9, the Examiner has asserted that the use of the phrase "a degenerate cell of the immune system" makes claim 14 unclear. A person of skill, upon reading the specification and applying his or her knowledge, including his knowledge of the lexicon of cell biology, would understand that, under ordinary physiological conditions, cells of the immune system are "normal," not tumor cells, and that tumor cells, which exhibit numerous characteristics of immune cells, are considered to be abnormal, malfunctioning cells, and are referred to as "degenerate immune cells."

Finally, in Paper No. 9, the Examiner indicated that he believes the use of symbol "/" and the designation "S1'" in claim 8 to render claim 8 indefinite. A person of ordinary skill, upon review of the specification and application of the knowledge in the art with which he is charged, would understand that the symbol "/" is merely indicative of the processing cite of the peptide. The symbol "S1'" is simply an art accepted designation for an amino acid residue found downstream of a processing cite. *See, e.g.,* Fersht (1985) Enzyme Structure and Mechanism, 2nd ed., W.H. Freeman & Co., New York at pp. 29-30 (a copy of which is enclosed for the Examiner's review). Thus, to a person of skill in the art, claim 8 is neither ambiguous nor indefinite.

In view of the foregoing, it is respectfully requested that the Examiner's indefiniteness rejections be reconsidered and withdrawn.

XI. Rejection Under 35 U.S.C. § 103(a)

At pages 14-18, the Examiner has rejected claims 1-16, 19-27, 29, and 32-37 under 35 U.S.C. § 103(a) as being unpatentable over the combination of the following references:

(1) U.S. Patent No. 4,894,443 of Greenfield, *et al.*; taken in view of

(2) Lappi, *et al.*, J. Bio. Chem., 1994, 269 (17):12552-12558;

(3) Wu *et al.*, Gene, 1997, 190 (1):157-162; and

(4) Deitrich, *et al.*, Anti-Cancer Drugs, 1992, 3:507-511; or

(5) Gabius, *et al.*, Anti-Cancer Res.,1992, 12:669-675.

As basis of the rejection, the Examiner asserts that Greenfield teaches the preparation of "recombinant conjugate toxins, including mistletoe comprising an enzymatically active domain . . . an intracellular cleavage site, a translocation or internalization facilitating domain . . ., a polypeptide spacer, and a target cell binding moiety . . . thereby teaching nucleic acids (*e.g.* DNA and RNA), vectors, host cells, fusion proteins, and methods of making fusion proteins." The Examiner asserts that the Greenfield enzymatically active domain encompasses an effector module, the intracellular cleavage site encompasses a processing module, the translocation domain encompasses a modulating module, and the target cell binding moiety encompasses a targeting module. The Examiner concedes that Greenfield does not teach the use of basic fibroblast growth factor as a targeting module, nor does it teach the vector pT7, the affinity module, or the claimed mistletoe lectin DNA or cDNA sequences *per se*.

The Examiner also asserts that Lappi teaches use of the plasmid pT7 for purposes of cloning an expression of fusion proteins. Further, according to the Examiner, Lappi teaches the use of basic fibroblast growth factor "within the context of a fusion protein" encompassing a targeting module.

With respect to Deitrich and Gabius, the Examiner asserts that Deitrich teaches the N-terminal sequences of several mistletoe lectin A chains which have "100 % identity" to the N-terminal sequence of MLA in the instant application. Similarly, the Examiner asserts that Gabius teaches the N-terminal sequences of both mistletoe lectin A and B chains which have "100 % identity" to the N-terminal sequences of MLA and MLB in the instant application.

Finally, the Examiner asserts that Wu teaches use of an in-frame 6x His tag (according to the Examiner, encompassing the affinity module) in a nucleic acid sequence encoding the recombinant *gfp* cDNA fusion protein.

Therefore, according to the Examiner, it would have been obvious to a person of ordinary skill in the art to apply the teachings of the four secondary references to those of Greenfield to arrive at the present invention. In particular, the Examiner specifies that "given the teachings of Greenfield to apply mistletoe immunotoxins," one of ordinary skill would have been motivated to substitute the nucleic acids disclosed in Deitrich and Gabius into the disclosure of Greenfield and, given the teachings in the art encompassing the uses of immunotoxic fusion

proteins to treat various conditions and diseases, a person of ordinary skill would have been motivated to make fusion proteins to target various cells, including the cells set forth in claims 9-14. Further, given the teachings of Lappi to use BFGF as a targeting molecule to treat tumors, one of skill in the art would have been motivated to substitute the FGF targeting moiety into the Greenfield immunotoxins comprising mistletoe. The applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness based upon a combination of references, the Examiner must demonstrate: (1) that the combination teaches or suggests each element of the claimed invention; (2) that a person of ordinary skill would have been motivated to make the combination proposed by the Examiner; and (3) that a person of ordinary skill would have had a reasonable expectation that such combination would have been successful. In the present situation, the Examiner has failed to meet all of these elements.

The present invention, in its broadest aspect, is a nucleic acid molecule encoding a fusion protein. The fusion protein comprises at least an effector module which is intracellularly cytotoxic, and comprises a mistletoe lectin A chain, a fragment thereof, or a derivative thereof, having a specific nucleotide sequence. The nucleic acid molecule of the invention also encodes a processing module having specific properties, and which comprises specific nucleotide and/or amino acid sequences. Finally, the nucleic acid molecule of the present invention also includes a portion encoding a targeting module.

Greenfield discloses a conjugate including three polypeptide component parts. First, the immunotoxin conjugate of Greenfield contains a cytotoxic component. The cytotoxic component of the Greenfield conjugate may contain an intracellular cleavage site and/or an internalization facilitating (or translocation) domain. This cytotoxic component may be the A chain of a bacterial or plant toxin, or may be a natural protein that has enzymatic activity similar to the A chain of a bacterial plant or toxin. Examples of such A chains provided by Greenfield are diphtheria A chain, exotoxin A chain (from *Pseudmonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurates fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAP1, PAP2, and PAP-S), momordin, curcin, crotin, gelonin, mitogellin, restrictocin, phenomycin, and enomycin. Col. 7, lines 34-46. While in the description of the prior art section of the Greenfield patent, "mistletoe" is listed as a bacterial and plant toxin (col. 1, line 18), it is <u>not</u> taught as a toxin for use in the Greenfield conjugate.

As a second component, the Greenfield conjugate contains a "specific binding moiety," which is an antibody or a fragment of an antibody, that is covalently linked to the

remainder of the conjugate (termed the "non-binding fragment"). Finally, the Greenfield conjugate includes a polypeptide spacer, designed so as to permit the cytotoxic portion of the molecule ready access to the cell membrane, and provide proper geometry for the cytotoxic activity.

Greenfield also discloses DNA sequences encoding the spacer polypeptide and the cytotoxic component of the plant or bacterial toxin. Neither a nucleotide sequence, nor an amino acid sequence containing all three of the Greenfield components is taught or suggested in Greenfield.

Lappi teaches a fusion protein containing the full length sequences of basic fibroblast growth factor (FGF-2) and the ribosome-inactivating protease resistant, protein saporin. According to Lappi, the resultant fusion protein showed cytotoxicity *in vitro*.

Wu discloses baculovirus expression vectors, such as pT7, containing *gfp* as a reporter gene. The expression vectors are constructed to contain an in-frame 6x His tag between the *gfp* cDNA and the multiple cloning site, to allow for purification of the fusion protein on an agarose matrix. An unspecific "gene of interest" can be cloned into the vectors described in Wu and expressed in insect cells using the baculovirus expression system.

Deitrich discloses the results of sequence analysis of the N-terminal of MLA chain (30 amino acid residues). Contrary to the Examiner's assertion, the amino acid sequence does not have "100 % identity" with that of the present invention. There is a one amino acid residue difference at residue 30, as shown in Deitrich.

Gabius discloses the amino-terminal sequences of the carbohydrate-binding B chain (20 amino acid residues) and the toxic A chain (28 amino acid residues) of ß-galactoside-specific lectin from mistletoe (ML-1).

The combination suggested by the Examiner does not teach or suggest each element of the invention as claimed. In particular, Greenfield does not teach a nucleotide including a fusion protein that comprises an effector module, a processing module, and a targeting module, as is recited in the present application. Greenfield discloses a polypeptide conjugate. The conjugate comprises a cytotoxic portion (which itself may include an intracellular cleavage site and/or a translocation domain), a spacer polypeptide, and a specific binding moiety, which is an antibody or a fragment of an antibody. Greenfield teaches a DNA sequence encoding a cytotoxic component and a spacer polypeptide ("a fusion protein"); however, Greenfield does not teach a nucleic acid molecule encoding the cytotoxic component, the specific binding moiety, and the spacer polypeptide. Neither the addition of Lappi, Gabius,

Deitrich, or Wu, remedies this deficiency. Lappi discloses a fusion protein of bFGF and saporin. Gabius and Deitrich disclose portions of the MLA and MLB amino acid sequence, which are similar to that disclosed in the present invention, and Wu discloses a baculovirus expression vector encoding, in part, a span of six consecutive histidines (6x His tag).

Further, there is no motivation in the art to make the combination as the Examiner has suggested. While mistletoe toxin is listed as a plant toxin in the background section of Greenfield, the Greenfield conjugate does not use any portion of mistletoe toxin as its cytotoxic component. In view of this omission, a person of ordinary skill would have been discouraged from including the toxin in the conjugate of the Greenfield invention, and would therefore not have combined Deitrich and Gabius. Further, because of this omission, there would have been no reasonable expectation that such combination would be successful.

Accordingly, for at least the reasons above, it is requested that the Examiner reconsider and withdraw the 37 U.S.C. § 103(a) rejection based upon the combination of Greenfield, Lappi, Deitrich/Gabius, and Wu.

CONCLUSION

In view of the remarks and amendments above, it is respectfully submitted that the claims of the invention are fully compliant with 35 U.S.C. § 112. Additionally, in view of the remarks, it is submitted that the claims are fully distinguished over all cited art. Accordingly, reconsideration and allowance of the claims are earnestly solicited at the earliest opportunity.

Respectfully submitted,

JÜRGEN ECK *et al.*

22 april 2002
(Date)

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Enclosures:
- *Petition for Extension of Time (3 months)*
- *Marked-Up Version of the Specification*
- *Marked-Up Version of the Claims*
- *Marked-Up Version of the Abstract*
- *Replacement Sequence Listing (paper and computer readable)*
- *Statement Under 37 C.F.R. § 1.821 et seq.*
- *Complete Set of Pending Claims (Ordered)*
- *The Oxford Dictionary of Biochemistry and Molecular Biology, Smith et al., Eds., Oxford University Press, 1997, p.p. 161*
- *Golub et al., Immunology: A Synthesis, 2nd ed., Sinaur Assoc., Inc., Sunderland, Massachusetts (1991), p.p. 7-8*
- *Fersht (1985) Enzyme Structure and Mechanism, 2nd ed., W.H. Freeman & Co., New York, 29-30*

Marked-Up Version of Specification

U.S. Patent Application No. 09/347,064

Please note that use of underlining indicates insertions and use of brackets indicates deletions.

Paragraph at page 25, lines 16-26:

-- In another preferred embodiment of the nucleic acid molecule according to the invention, the affinity module is a [histidine sequence, thioredoxin, Strep-Tag, T7-Tag, FLAG-Tag, maltose-binding protein or GFP (Green Fluorescent Protein)] histidine sequence, thioredoxin, a maltose-binding protein, or GFP (green fluorescent protein). Additionally, the affinity module may be *STREP-TAG®*, available from IBA GmbH, Gottingen, Germany, a peptide having highly selective binding affinity for engineered streptavidin; the FLAG peptide (DYKKDDDK[SEQ ID NO.: 39]), available as FLAG-TAG® from Strategene, Corp., La Jolla, California, U.S.A; or T7-TAG®, a T7 peptide that is an 11 amino acid gene leader peptide, available commercially from CN Biosciences Corp., Darmstadt, Germany. The affinity module is a peptide sequence which is characterized by a ligand binding specificity or by the presence of suitable epitopes which allows a selective purification preferably by affinity chromatography methods, e.g., by way of immobilized ligands or immobilized antibodies. Such affinity modules always have the property of binding ligands very specifically and with high binding constants, which in turn are preferably coupled as ligands to chromatographic matrices. In this way, highly purified fusion proteins from lysates or cell supernatants can be produced using processes with only few steps. --

Marked-Up Version of Claims 1, 15, 18, 29, 37

U.S. Patent Application No. 09/347,064

Please note that use of underlining indicates insertions and use of brackets indicates deletions.

1. (Amended) A nucleic acid molecule encoding a fusion protein which comprises

(a) an effector module which is intracellularly cytotoxic, the effector module comprising one of [the] a mistletoe lectin A chain, a fragment thereof, and a derivative thereof, wherein the mistletoe lectin A chain is encoded by a nucleic acid molecule selected from the group consisting of:

(i) a nucleic acid molecule which has a nucleotide sequence encoding at least a fragment of a protein having the amino acid sequence SEQ ID NO: 2;

(ii) a nucleic acid molecule having the nucleotide sequence of at least a fragment of SEQ ID NO: 1;

(iii) a nucleic acid molecule which hybridizes with the nucleic acid molecule of (i) or (ii); and

(iv) a nucleic acid molecule which is degenerate with respect to the nucleic acid molecule of (iii);

(b) a processing module which is covalently linked to the effector module and which comprises a recognition sequence for a protease, wherein the processing module comprises one of [the] a mistletoe lectin propeptide, a fragment thereof, and a derivative thereof, and wherein the mistletoe lectin propeptide is encoded by a nucleic acid molecule selected from the group consisting of:

(i) a nucleic acid molecule which has a nucleotide sequence encoding at least a fragment of a protein having the amino acid sequence SEQ ID NO: 6;

(ii) a nucleic acid molecule having the nucleotide sequence of at least a fragment of SEQ ID NO: 5;

(iii) a nucleic acid molecule which hybridizes with the nucleic acid molecule of (i) or (ii); and

(iv) a nucleic acid molecule which is degenerate with respect to the nucleic acid molecule of (iii); and

(c) a targeting module which is covalently linked to the processing module and which specifically binds to the surface of a cell, thereby mediating internalization of the fusion protein into the cell.

15. (Twice amended) The nucleic acid molecule of claim 7, wherein the affinity module comprises a portion selected from the group consisting of a [histidine sequence, thioredoxin, Strep-tag®, T7 tag®, FLAG®-tag, maltose binding protein, and green fluorescent protein] histidine sequence, thioredoxin, maltose-binding protein, green fluorescent protein, SEQ ID NO.: 39, and an 11 amino acid T7 gene leader peptide.

17. (Amended) The nucleic acid molecule of claim 16, wherein the mistletoe lectin B chain has at least one amino acid exchange at an amino acid position selected from the group consisting of positions 23, 38, [68, 70, 75], 79, 235, and 249.

18. (Amended) The nucleic acid molecule of claim 17, wherein the exchange is selected from the group consisting of substitution of A at position D23, substitution of A at position W38, substitution of A at position D235, and substitution of A at position Y249[, substitution of S at position Y68, substitution of S at position Y70, substitution of S at position Y75, substitution of S at position F79].

33. (Amended) A kit, comprising at least one of

(a) a vector which comprises [a] the nucleic acid molecule of claim 1; and

(b) a vector which comprises [a] the nucleic acid molecule of claim [1]7;

and a vector which comprises a nucleic acid molecule encoding a modulator which modulates the intracellular cytotoxicity of the effector module of (a) and/or (b).

34. (Amended) A nucleic acid molecule encoding a fusion protein which comprises

(a) an effector module which is intracellularly cytotoxic, the effector module comprising one of [the] a mistletoe lectin A chain, a fragment thereof, and a derivative thereof, wherein the mistletoe lectin A chain is encoded by a nucleic acid molecule selected from the group consisting of:

(i) a nucleic acid molecules which has a nucleotide sequence encoding at least a fragment of a protein having the amino acid sequence SEQ ID NO: 2;

(ii) a nucleic acid molecule which has the nucleotide sequence of at least a fragment of SEQ ID NO: 1;

(iii) a nucleic acid molecule which hybridizes with the nucleic acid molecule of (i) or (ii); and

(iv) a nucleic acid molecule which is degenerate with respect to the nucleic acid molecule of (iii);

(b) a processing module which is covalently linked to the effector module and which comprises a recognition sequence for a protease; and

(c) a targeting module which is covalently linked to the processing module and which specifically binds to the surface of a cell, thereby mediating internalization of the fusion protein into the cell.

35. (Amended) The nucleic acid molecule of claim 34, wherein the processing module comprises one of [the] a mistletoe lectin propeptide having SEQ ID NO: 6, a fragment thereof, and a derivative thereof.

36. (Amended) A nucleic acid molecule encoding a fusion protein which comprises

(a) an effector module which is intracellularly cytotoxic;

(b) a processing module which is covalently linked to the effector module and which comprises a recognition sequence for a protease, wherein the processing module comprises one of [the] a mistletoe lectin propeptide, a fragment thereof, and a derivative thereof,

and wherein the mistletoe lectin propeptide is encoded by a nucleic acid molecule selected from the group consisting of:

(i) a nucleic acid molecule which has a nucleotide sequence encoding at least a fragment of a protein having the amino acid sequence SEQ ID NO: 6;

(ii) a nucleic acid molecule which has the nucleotide sequence of at least a fragment of SEQ ID NO: 5;

(iii) a nucleic acid molecule which hybridizes with the nucleic acid molecule of (i) or (ii); and

(iv) a nucleic acid molecule which is degenerate with respect to the nucleic acid molecules mentioned in (iii); and

(c) a targeting module which is covalently linked to the processing module and which specifically binds to the surface of a cell, thereby mediating internalization of the fusion protein into the cell.

37. (Amended) The nucleic acid molecule of claim 36, wherein the effector module comprises one of [the] a mistletoe lectin A chain having SEQ ID NO: 2, a fragment thereof, and a derivative thereof.

the sequence

Attorney Docket No.
9282-5 (B 3521 US)

Marked-Up Version of Abstract of Disclosure

U.S. Patent Application No. 09/347,064

Shown below are the changes to the Abstract of Disclosure. Please note that deletions are indicated by brackets and insertions are indicated by underlining.

-- The invention relates to nucleic acid molecules which encode fusion proteins which contain as components at least one effector module, a processing module and a targeting module. The nucleic acid molecules according to the invention preferably also encode a modulator module and/or an affinity module. The invention furthermore relates to vectors containing these nucleic acid molecules, hosts transformed with the vectors according to the invention, fusion proteins encoded by nucleic acids according to the invention or produced by the hosts according to the invention as well as to medicaments containing the polypeptides or vectors according to the invention. [These medicaments are particularly significant for the therapy of diseases associated with a pathological reproduction and/or increased activity of cell populations. A temporary, periodic and strong proliferation, infiltration and immune activity of cells of the immune system is found in autoimmune diseases and allergies, the specificity of these immune cells being due to their reaction to a particular antigen or allergen. These medicaments may also be advantageously used for treating tumors. The polypeptides and vectors described in the present invention may be used to develop medicaments and to test toxin activity-modulating factors.] The invention thus also concerns corresponding processes, uses and kits. [The modules, with the exception of the affinity and the targeting module, are preferably encoded by nucleic acids extracted or derived from the mistletoe lectin proprotein coding sequence.] –